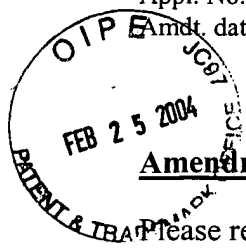


Amdt. dated February 20, 2004

**Amendments to the Specification:**

Please replace the paragraph beginning on page 7, line 27, with the following amended paragraph:

Further, the present invention demonstrated that addition of a FLAG tag (DYKDDDDK) (~~residues 27-34 of SEQ ID NO:6~~) **(SEQ ID NO:61)** to the C-terminus of Humanin does not affect the neuroprotective action thereof (Example 3). Furthermore, even when the four C-terminal amino acids (KRRA) (~~residues 21-24 of SEQ ID NO:5~~) **(SEQ ID NO:62)** of Humanin were substituted with other amino acids, a neuroprotective action equivalent to that of the original Humanin was present in the substituted polypeptide (Example 6). These facts demonstrate that polypeptides with equivalent or higher neuroprotective action to can be prepared by introducing mutations to the amino acid sequence of Humanin, HNG, AGA-HNG, and substituted forms thereof, wherein the C8 is substituted with a basic amino acid.

Please replace the paragraph beginning on page 9, line 2 with the following amended paragraph:

The polypeptide of the present invention includes polypeptides that suppress neuronal death associated with Alzheimer's disease (AD) and having an amino acid sequence consisting of Formula (I):

Pro-Xn<sub>1</sub>-(Cys/bXaa)-(Leu/Arg)-Xn<sub>2</sub>-Leu-Thr-(Gly/Ser)-Xn<sub>3</sub>-Pro (I) (~~SEQ ID NO:61~~) **(SEQ ID NO:63)**.

Herein, "Cys/bXaa" indicates Cys or a basic amino acid; "(Leu/Arg)" indicates Leu or Arg; "(Gly/Ser)" indicates Gly or Ser; and Xn<sub>1</sub>, Xn<sub>2</sub>, and Xn<sub>3</sub> independently indicate arbitrary amino acids not more than 10 residues, respectively. A polypeptide that has the amino acid sequence as above may be also expressed as:

Pro-(Xaa)<sub>1-10</sub>-(Cys/bXaa)-(Leu/Arg)-(Xaa)<sub>1-10</sub>-Leu-Thr-(Gly/Ser)-(Xaa)<sub>1-10</sub>-Pro (~~SEQ ID NO:61~~) **(SEQ ID NO:64)** (II)

(wherein Xaa indicates an arbitrary amino acid; "(Xaa)<sub>m-n</sub>" indicates m to n residues of arbitrary amino acids; "bXaa" indicates a basic amino acid; "Cys/bXaa" indicates Cys or a basic amino acid; "(Leu/Arg)" indicates Leu or Arg; and "(Gly/Ser)" indicates Gly or Ser).

Please replace the paragraph beginning on page 9, line 18 with the following amended paragraph:

Basic amino acids refer to amino acids in which its R group (side chain) is positively charged at pH7.0. Examples of natural basic amino acids include Arg, Lys, and His. The amino acid sequences of a polypeptide of this invention that has Arg, Lys, or His as the basic amino acids can be represented, for example, as:

Pro-X<sub>N1</sub>-(Cys/Arg/Lys/His)-(Leu/Arg)-X<sub>N2</sub>-Leu-Thr-(Gly/Ser)-X<sub>N3</sub>-Pro (~~SEQ ID NO:62~~)

(SEQ ID NO:65)

(III)

(wherein “(Cys/Arg/Lys/His)” indicates Cys, Arg, Lys, or His; “(Leu/Arg)” indicates Leu or Arg; “(Gly/Ser)” indicates Gly or Ser; and X<sub>N1</sub>, X<sub>N2</sub>, and X<sub>N3</sub> independently indicate arbitrary amino acids not more than 10 residues, respectively). Herein, Arg and Lys are particularly preferable as the basic amino acid at this position.

Please replace the paragraph beginning on page 10, line 9, with the following amended paragraph:

Preferably, the sequence of X<sub>N1</sub> includes, for example, sequences consisting of (Arg/Ala)-(Gly/Ala)-(Phe/Ala)-(Ser/Ala) (~~SEQ ID NO:96~~)(SEQ ID NO:66), and sequences with conservative substitution thereof. Herein, for example, “Arg/Ala” indicates Arg or Ala (“/” indicates that it is either one of the residues; the same is indicated throughout the description herein). Examples of such sequences include Arg-Gly-Phe-Ser (~~SEQ ID NO:63~~)(SEQ ID NO:67), Ala-Gly-Phe-Ser (~~SEQ ID NO:64~~)(SEQ ID NO:68), Arg-Ala-Phe-Ser (~~SEQ ID NO:65~~)(SEQ ID NO:69), Arg-Gly-Ala-Ser (~~SEQ ID NO:66~~)(SEQ ID NO:70), Arg-Gly-Phe-Ala (~~SEQ ID NO:67~~)(SEQ ID NO:71), and so on. Other examples include Arg-Gly-Ala-Ala (~~SEQ ID NO:68~~)(SEQ ID NO:72), Arg-Ala-Phe-Ala (~~SEQ ID NO:69~~)(SEQ ID NO:73), Arg-Ala-Ala-Ser (~~SEQ ID NO:70~~)(SEQ ID NO:74), Arg-Ala-Ala-Ala (~~SEQ ID NO:71~~)(SEQ ID NO:75), Ala-Gly-Phe-Ala (~~SEQ ID NO:72~~)(SEQ ID NO:76), Ala-Gly-Ala-Ser (~~SEQ ID NO:73~~)(SEQ ID NO:77), Ala-Gly-Ala-Ala (~~SEQ ID NO:74~~)(SEQ ID NO:78), Ala-Ala-Phe-Ser (~~SEQ ID NO:75~~)(SEQ ID NO:79), Ala-Ala-Phe-Ala (~~SEQ ID NO:76~~)(SEQ ID NO:80), Ala-Ala-Ala-Ser (~~SEQ ID NO:77~~)(SEQ ID NO:81), Ala-Ala-Ala-Ala (~~SEQ ID NO:78~~)(SEQ ID NO:82), and such. Conservative substitution can be exemplified by substitution within a group of amino

acids, corresponding to conservative substitution, which will be described later. On the other hand, the sequence of  $X_{n2}$  preferably includes, for example, sequences consisting of (Leu/Ala)-(Leu/Ala), and sequences with conservative substitution thereof. Such sequences include Leu-Leu, Ala-Leu, Leu-Ala, and such. Ala-Ala can be also exemplified as such sequences.

Furthermore, the sequence of  $X_{n3}$  preferably includes, for example, sequences consisting of (Glu/Ala)-(Ile/Ala)-(Asp/Ala)-(Leu/Ala) (~~SEQ ID NO:79~~)(**SEQ ID NO:83**), and sequences with conservative substitution thereof. Such examples include Glu-Ile-Asp-Leu (~~SEQ ID NO:80~~)(**SEQ ID NO:84**), Ala-Ile-Asp-Leu (~~SEQ ID NO:81~~)(**SEQ ID NO:85**), Glu-Ala-Asp-Leu (~~SEQ ID NO:82~~)(**SEQ ID NO:86**), Glu-Ile-Ala-Leu (~~SEQ ID NO:83~~)(**SEQ ID NO:87**), Glu-Ile-Asp-Ala (~~SEQ ID NO:84~~)(**SEQ ID NO:88**), and so on. Other examples are Glu-Ile-Ala-Ala (~~SEQ ID NO:85~~)(**SEQ ID NO:89**), Glu-Ala-Asp-Ala (~~SEQ ID NO:86~~)(**SEQ ID NO:90**), Glu-Ala-Ala-Leu (~~SEQ ID NO:87~~)(**SEQ ID NO:91**), Glu-Ala-Ala-Ala (~~SEQ ID NO:88~~)(**SEQ ID NO:92**), Ala-Ile-Asp-Ala (~~SEQ ID NO:89~~)(**SEQ ID NO:93**), Ala-Ile-Ala-Leu (~~SEQ ID NO:90~~)(**SEQ ID NO:94**), Ala-Ile-Ala-Ala (~~SEQ ID NO:91~~)(**SEQ ID NO:95**), Ala-Ala-Asp-Leu (~~SEQ ID NO:92~~)(**SEQ ID NO:96**), Ala-Ala-Asp-Ala (~~SEQ ID NO:93~~)(**SEQ ID NO:97**), Ala-Ala-Ala-Leu (~~SEQ ID NO:94~~)(**SEQ ID NO:98**), Ala-Ala-Ala-Ala (~~SEQ ID NO:95~~)(**SEQ ID NO:99**), and so on. The sequences of  $X_{n1}$ ,  $X_{n2}$ , and  $X_{n3}$  may be selected from arbitrary combinations.

**Amendments to the Drawings:**

Please replace the original drawing sheets comprising Figures 1 and 25 with the enclosed replacement drawing sheets which also comprise Figures 1 and 25. Annotated copies of the original drawing sheets comprising Figures 1 and 25 are also enclosed.

Attachment: Two Replacement Sheets  
Two Annotated Sheets Showing Changes